Hematopoietic Stem Cell Engraftment in the Endosteal Niche is Dependent Upon the Calcium Sensing Receptor

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Anatomic localization of adult mammalian hematopoietic stem cells (HSC) adjacent to bone has led to identification of the osteoblast, as a key participant in the HSC niche. We reasoned that other components of bone may contribute to the unique ability of the bone marrow to provide for long term multilineage blood cell production. Conceptually dividing bone into three major components i.e. cell, extracellular matrix and mineral, we have systematically evaluated candidate participants of niche function. Due to previously identified high concentrations of ionic calcium found at the trabecular surface where bony remodeling occurs and where stem cells have been found to reside, we evaluated whether stem cells may respond to the local high calcium through the calcium sensing receptor (CaR). Activation of this G-protein coupled receptor has been previously noted to modify migration, proliferation, differentiation and apoptosis in some epithelial cells and migration in monocytes. We demonstrated its expression in stem cell enriched subsets of normal murine bone marrow and evaluated its function using a CaR deficient mouse. $CaR^{-/-}$ mice demonstrated markedly reduced HSC in the bone marrow, but increased frequencies of primitive cells in the circulation and spleen. The development of HSC appeared intact as the number, proliferation and differentiation of fetal liver derived HSC were normal. However, $CaR^{-/-}$ fetal liver HSC used as donor cells in bone marrow competitive repopulation assays were dramatically ineffective at engrafting the bone marrow. This engraftment defect was not due to altered chemotaxis to SDF-1 *in vitro*, decreased expression of surface receptors associated with adhesion or abnormal homing to the bone marrow as a whole *in vivo*. Rather, primitive hematopoietic $CaR^{-/-}$ cells appeared to demonstrate aberrant localization specifically to the HSC enriched endosteal surface *in vivo*, which correlated with aberrant expression of previously defined mediators of stem cell function. Therefore, functional engagement of stem cells with the bone marrow niche appears to depend upon activation of the CaR, linking the unique mineral context of bone with the function of bone marrow.